Immortal Time Bias and the Use of IVC Filters

We commend the RIETE (Computerized Registry of Patients with Venous Thromboembolism) group for attempting to analyze the benefits of use of an inferior vena cava (IVC) filter after acute pulmonary embolism (PE) using their large prospectively collected registry (1). Their propensity-matched analysis showed a lower risk-adjusted PE-related mortality rate in patients who received an IVC filter compared those who did not. However, we wish to point out a significant source of bias in this observational study that cannot be adjusted for with the use of propensity matching.

The bias we refer to is termed "immortal time bias" (2). This bias is frequently encountered when analyzing the effectiveness of an intervention, such as use of an IVC filter, when using observational data. The placement of a filter also depends on meeting some clinical criteria, having a physician available to place the filter, and the patient's clinical condition. In more critically ill patients, insertion of a filter may not be possible and death may occur before placement of the filter. In analyzing the data, if simply comparing the outcomes of patients with an IVC filter versus those without, the results are biased. All patients who received a filter were alive at the time of the procedure (hence, they were "immortal" up to the time the filter was placed), whereas the patients who did not receive a filter included those who may have died before a filter could be placed. This distinction between the 2 groups is important; upwards of 30% of PE-related mortality occurs within the first 24 h of hospitalization (3). In the study by Muriel et al. (1), in the patients who received an IVC filter, the authors started the clock on the primary outcome of 30-day mortality on the day the filter was placed; however, in the patients who did not receive a filter, it was considered to be when anticoagulation was started. A better way of analyzing these data would be to use the admission date or the date of diagnosis of PE as the anchor time and model death due to PE by using a Cox proportional hazard model, entering use of an IVC filter as a time-dependent covariate. The hazard associated with use of a filter is compared with the hazard of not using a filter in patients who are alive on the same day. Using this methodology, all patients who were not treated with a filter but who died early after diagnosis of PE are excluded from calculation of the relative hazard associated with use of a filter. Alternatively, patients could be matched on both propensity score and being alive on the day of placement of the filter, thereby excluding those who died before the intervention could be completed. We suggest that the authors use one of these suggested methodologies to determine if the hazard ratio for PE-related mortality is similar or significantly different between those with and without a filter.

The authors raise several interesting points, but we ultimately agree with the conclusion of Dr. Morris in the accompanying editorial (4). The only way to truly settle the controversial issue of whether filters are beneficial in patients who cannot be anticoagulated is by conducting a well-designed clinical trial. However, performing such a trial will be difficult. Informed consent will have to be obtained quickly, followed by rapid randomization and expeditious insertion of the IVC filter. Until that time, clinicians must try to make inferences from observational studies that have unmeasured confounders as well as immortal time bias. We believe the results of such analyses should not have any major impact on venous thromboembolism guidelines or clinical practice.

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REPLY: Immortal Time Bias and the Use of IVC Filters

We thank Drs. Fernandes and White for their thoughtful comments about our registry-based retrospective cohort study of patients with acute venous thromboembolism (1). We agree that the start time of follow-up and treatment status in the design and analysis of our study (1) might have introduced

immortal time bias (2) and subsequently affected the results of the study. To address this concern, as suggested in their letter to the editor, we reanalyzed the data after matching for propensity score and being alive on the day of filter placement. We identified 8 patients (8 of 344 [2.3%]; 95% confidence interval [CI]: 0.7% to 3.9%) in the control group who died before insertion of the filter, and we removed the matched pairs from the reanalysis. The propensity-based matching of patients yielded 336 patients with an inferior vena cava filter and 336 patients without a filter. We did not detect a difference in mortality between patients who received a filter and those who did not (6.8% vs. 8.9%; risk difference: −2.1% [95% CI: −6.3% to 2.0%]; p = 0.32), although the clinically relevant trend favored treatment with a filter. Analysis of propensity score-matched pairs showed a statistically significant lower risk of pulmonary embolism-related mortality for patients with a filter compared with those without a filter (0.9% vs. 3.3%; risk difference: −2.4% [95% CI: −4.9% to −0.2%]; p = 0.04). Thus, after addressing the concerns outlined in the letter to the editor, we have results and conclusions similar to those described in the study report (1).

A randomized trial is a powerful tool because it enables clinical researchers to evaluate the efficacy of therapies without worrying about unmeasured confounders and some types of bias such as immortal time bias. Although we agree that a randomized controlled trial would provide the strongest evidence regarding the efficacy and safety of inferior vena cava filters in patients with an acute venous thromboembolism and a contraindication to anticoagulation, the ethical issues associated with using a no-treatment control group would likely prevent the performance of such a trial. If it is not feasible to conduct a well-designed randomized trial, investigators may use observational studies to examine and infer treatment effects. Although retrospective observational studies may have various types of bias, propensity scores may reduce the impact of any imbalance in pre-treatment patient characteristics and may address concerns about confounding. Studies have found fairly good agreement between treatment effects in propensity score-based observational cardiovascular studies compared with those in randomized trials (3).

In conclusion, despite its inherent limitations, our study shows provocative results regarding the potential survival benefit associated with use of inferior vena cava filters in patients with acute venous thromboembolism and absolute or relative contraindications to anticoagulant therapy. We encourage further assessment of the validity of these findings.

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The Murky World of Effective Dose for Cardiovascular CT

We read with interest the excellent report by Einstein et al. (1) and the accompanying pragmatic editorial (2). We support the laudable aim of involving patients in the discussion of radiation exposure as part of the clinical decision process, but we wish to highlight a couple of areas for cardiovascular computed tomography (CT) specifically that require expert consensus to ensure this process is robust.

Dose calculation in cardiovascular CT is a complex field of medical physics, and the lack of clarity on even the fundamentals clearly needs to be addressed. First, the determination of an effective dose for procedures such as cardiovascular CT remains controversial, while the lack of cardiovascular CT dose reference levels and current benchmarking of institutional practice against these makes generalization of dose potentially meaningless.

Several different conversion factors are currently used in published reports when converting dose-length product into an effective radiation dose (in mSv) delivered to a patient. Aside from the fact that these conversion factors were not designed to be